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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,614	11/15/2001	David Botstein	P2730P1C29	7398

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,614	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126, 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Remarks, submitted 5 January 2007, have been entered. Claims 1-118, 127 and 128 are cancelled.

Claims 119-126 and 129-131 are under examination in the Instant Application.

Maintained/New Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

The following is a quotation of 35 U.S.C. 101:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 3-19 of the previous Office Action (5 October 2006). Claims 119-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (5 October 2006), one skilled in the art clearly would not know how to

use the claimed invention.

Applicants argue (5 January 2007, page 4 and throughout) that the results presented in the instant Specification are enabling for the polypeptide of SEQ ID NO: 349. They argue that the PRO1097 polypeptide is overexpressed in lung and colon tumors. They point to Table 8 of the Specification to argue that the PRO1097 polypeptide is overexpressed in lung and colon tissue relative to a blood control and that it thus has substantial and specific Utility.

Applicants' arguments (5 January 2007) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the Specification suggests that the PRO1097 peptide may be overexpressed in lung and colon tumor tissue, but they give no *specific* or *substantial* information about the disclosed PRO1097 peptide or nucleic acid. There is no evidence regarding whether or not the PRO1097 polypeptide has a specific function in an organism, aside from its overexpression in lung and colon tumor tissue. Applicants refer to the gene expression experiment of the Specification (citing delta-Ct values), however this gives no *specific* or *substantial* information about the claimed PRO polypeptide.

Further research needs to be done to determine whether the amplification of the PRO1097 gene supports a role for the peptide in any tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
>
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed PRO1097 polypeptide is overexpressed in lung and colon tumor tissue is not substantial. Utility requires that the skilled artisan be able to use the claimed invention. The specification does not provide a specific and substantial or a well-established use. A utility of being overexpressed in lung and colon tumor tissue is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use. This is not a substantial utility. The instant Specification does not provide any evidence that indicates a specific or substantial real-world use. Applicants have provided no indication of a condition caused by a mutant version of this polypeptide, or any conditions treated by adding this polypeptide. The only thing Applicants teach is that the PRO1097 gene is more highly expressed in some tissues. Without more specifics about the claimed species of polypeptide, expression level range for normal and tumor tissues, types of tissue that should be studied as well as other questions about underlying mechanisms, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary.

Applicants argue that Taqman™ PCR technology all rely on the dogma that a change in PCR cycle units represents a 2-fold amplification of a gene and that if a gene product is over-or-under-expressed, it provides more accurate tumor classification and hence better determination

of suitable therapy (page 4, 5 January 2007). This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1097 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1097 nucleic acid was amplified in some lung or colon cancers and some normal tissues, to a minor degree, by about 2-fold. No mutation or translocation of PRO1097 has been associated with lung tumors or colon tumors. It is not known whether PRO1097 is expressed in other normal tissues besides normal lung or colon tissue, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1097 is amplified in a small number of samples, and invite the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al. (of record), the issue is simply not predictable, and the specification presents a mere invitation to experiment. More importantly, however: there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not.

Applicants argue that Bieche et al. (submitted with the Response of 22 August 2005) used normal leukocyte DNA derived from a small subset of breast cancer patients and note that the results of the study are consistent with those reported in the literature. Applicants conclude that the art demonstrates that pooled normal blood samples are considered to be a valid negative controls for gene amplification experiments.

Applicants' arguments have been fully considered but are not found to be persuasive. Specifically, although Pennica et al. and Pitti et al. compare gene amplification of specific genes in colon and lung tumors to pooled DNA from 10 healthy normal donors, Pennica et al. and Pitti et al. are not attempting to utilize the data generated from the experiments for diagnostic purposes (as is Example 143 of the instant application). Secondly, Bieche et al. is simply utilizing real-time PCR to validate an assay for the detection and determination of the copy numbers of the three most-frequently amplified genes in breast tumors (*myc, ccnd1*, and *erbB2*). Bieche et al. compare the results for 108 breast tumors with previous Southern-blot data for the same samples (abstract; page 662, column 1). The genes studied by Bieche et al. were already well-known in the art to be amplified in breast cancer. For this reason, it was not necessary to utilize matched normal tissue samples.

Regarding the instant application, the specification provides data purportedly showing a slight increase in DNA copy number in two different types of tumor tissue (lung and colon) of PRO1097. However, PRO1097 is novel and has not been characterized in the pre- or post-filing date art. It is not known whether PRO1097 is expressed in corresponding normal tissues, and what the relative levels of expression are. There is no structure/function analysis in the specification regarding the putative protein encoded by the PRO1097 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner cannot find any reason to suspect, that the protein encoded by the PRO1097 gene would confer any selective advantage on a cell expressing it. It has no known homology to any protein that would be expected to confer a selective advantage to a tumor cell. Additionally, gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested

empirically. The instant specification does not provide this additional information. Therefore, the skilled artisan would need to perform additional experiments to determine the function of the PRO1097 gene.

Applicants refer to the Declaration of Dr. Goddard (22 August 2005) to argue again that the blood control used in Example 30 is a well-accepted, informative and reliable control (p. 5 of Response). Thus, Applicants argue, the instant specification discloses a specific, credible and substantial utility for the PRO1097 polypeptide of the current application.

Applicants' arguments have been fully considered but have not been found to be persuasive. Utility requires that the skilled artisan be able to use the claimed invention. The specification does not provide a specific and substantial or a well-established use. A utility of being a diagnostic target for lung and colon tumors is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use. This is not a substantial utility. In Example 30, Applicants teach that PRO1097 was overexpressed in lung and colon tumor as compared to the blood control (see Table 8 of Specification). Rather, one of the issues is that there is no guidance in the specification as to how high the levels of overexpression are. The Declaration of Dr. Goddard does not teach the level of reproducibility or the level of reliability of the results. Neither the specification nor the Declaration provide any evidence that indicates what the differences were. If a clinician took a tissue sample from a patient with suspected cancer, what is the likelihood that when compared with normal tissue, the level of nucleic acid of SEQ ID NO: 348 from the patient would be higher? How many samples would be needed? What sensitivity would be needed? Would the

normal tissue have to be a pooled sample or could it be from a single individual? Applicants have provided no indication of the nature or number of samples that were used. The only thing Applicants teach is that the gene was "more highly expressed", and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of tumor tissue that can be used, and other questions, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary.

Furthermore, the Declaration does not provide data such that the examiner can independently draw conclusions. Only the conclusions of Dr. Goddard are provided in the declaration. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants again discuss the Polakis Declaration (filed under 37 CFR § 1.132, 5 July 2006) which states that approximately 200 gene transcripts were identified that are present in

human tumor cells at significantly higher levels than in control tissues and that antibodies have been developed that identify and could possibly be used to downregulate the PRO peptides. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. He characterizes the instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. Firstly, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1097 in tumor samples as contrasted to normal tissue samples: Only gene amplification data were presented. As discussed above, and in the previous Office Action (5 October 2006) this doubling of DNA levels in cancer tissue may be due to a doubling of chromosome number, an event that is very common in cancerous tissues. In addition, it has not been shown that RNA or protein levels are increased in these two cancers.

Applicants argue (Response, 5 January 2007, bottom of page 6) that even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Applicant argues that the disclosure of the PRO1097 peptide can be viewed as providing a public benefit. However, the instant Specification does not provide specific information about the PRO1097 nucleotides or peptides and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polynucleotides is not in currently available form, the asserted utility is not substantial.

35 USC § 112, first paragraph - Written Description.

Claims 119-123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at pp. 19-20 of the previous Office Action (5 October 2006). They have not removed references to amino acids having 80-99% sequence identity to the claimed PRO1097 polypeptide and Applicants were not in possession of all or a significant number of polypeptides that have 80-99% homology to SEQ ID NO: 349, while retaining the function of SEQ ID NO: 349.

Applicants discuss the legal standards applied when evaluating Written Description, stating that sufficiency of support under Written Description depends on whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject and cite relevant case law (In re Kaslow 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983), for example). However, In re Kaslow discussed the *timing* of the disclosure in a way sufficient to show that the applicant was in possession of the claimed invention. The examiner takes no issue with the discussion of general requirements for evaluating Written Description in this case or with the fact that Applicants are indeed in possession of SEQ ID NO: 349 in this Application. However, Applicants have not described or shown possession of all polypeptides 80-99% homologous to SEQ ID NO: 349, *that are functionally equivalent to SEQ ID NO: 349.* Nor have Applicants described a representative number of species that have 80-99% homology to SEQ ID NO: 349, such that it is clear that they

were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 349. It should be noted that SEQ ID NO: 349 is a naturally-occurring polypeptide, with only one member described.

As discussed in the previous Office Action (5 October 2006) even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1097 polypeptides, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product itself is required. Recitation of the phrase "wherein said polypeptide is overexpressed in lung and colon tumor cells..." (Amended claims, 5 January 2007), is not adequate to describe the PRO1097 polypeptide or the polynucleotides encoding the PRO1097 polypeptide, that have 80-99% homology to the PRO1097 polypeptide, since there was no reduction to practice to support the amended claims. Applicants made no variant polynucleotides or polypeptides, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from

the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire Later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
13 March 2007

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER